

Al^{III}-Calix[4]arene Catalysts for Asymmetric Meerwein-Ponndorf-**Verley Reduction**

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Supporting Information

ABSTRACT: Chiral Al^{III}-calixarene complexes were investigated as catalysts for the asymmetric Meerwein-Ponndorf-Verley (MPV) reduction reaction when using chiral and achiral secondary alcohols as reductants. The most enantioselective catalyst consisted of a new axially chiral vaulted-hemispherical calix[4] arene phosphite ligand, which attained an enantioselective excess of 99%. This ligand consists of two lower-rim hydroxyl groups, with the remaining two lower-rim oxygens directly connected to the phosphorus of the phosphite, which is derived from a chiral diol. The results emphasize the importance of the rigid calix[4]arene lower-rim substituents



and point to a possible role of a lower-rim chiral pocket and Lewis-basic phosphorus lone pairs in enhancing asymmetric hydride transfer.

KEYWORDS: MPV reduction, chiral, asymmetric hydride transfer, Lewis-acid catalysis, calixarene complexes, phosphite ligand

INTRODUCTION

The Meerwein-Ponndorf-Verley (MPV) reaction is a mild reduction method for ketones, which is catalyzed using nontoxic and earth-abundant main group elements—in this case, Lewis acidic $Al(III)^{1-4}$ —and can be directed to introduce asymmetric carbons in prochiral ketones. There are several applications of this reaction, including a stereoselective variant that has been recently used for the synthesis of pharmaceutical building blocks for anti-HIV therapeutics.³ In general, asymmetric MPV reduction can be tuned by using either a chiral alcohol as a sacrificial reductant or a chiral Lewis acid complex as a catalyst. Here, in this article, we investigate the essential catalyst structural features for asymmetric MPV reduction using Al(III)-calixarene complexes, in which the metal is placed in a chiral oxo environment. Our results demonstrate enantioselective Al-based catalysts for MPV reduction, which are among the few that accomplish this in the absence of chiral alcohol.^{5,6}

Our approach leverages lower-rim-substituted cone Al(III)tert-butylcalix[4] arene complexes, which are tunable. We recently demonstrated these complexes as highly active homogeneous-catalyst sites for MPV reduction.^{7,8} The Al-(III)-calixarene complex remained intact as observed using ¹H NMR spectroscopy during catalysis. The crucial role of the calixarene is to enforce active-site isolation in these catalysts, thereby avoiding aggregation of Al-alkoxide-type species, which leads to coordinatively saturated hexacoordinate Lewis acid sites, which are catalytically inactive. This class of catalyst is 2-fold more active per Al site compared with freshly prepared aluminum isopropoxide, and active-site isolation was characterized previously using ²⁷Al NMR spectroscopy both in homogeneous as well as in grafted Al(III)-calixarene sites on silica. ³ This class of catalyst bridges the homogeneousheterogeneous gap in that both homogeneous and grafted Al(III)-calixarene-on-silica variants of this molecular catalyst have the same per-site MPV activity. Also, in the case of the homogeneous catalyst, we demonstrated that the calixarene enabled synthesis of a molecular pocket, which affected accessibility and catalytic rate at the Al center.^{7,8} Here, we build on the tunability of calixarene-based catalysts, with the synthesis of chiral 1,3-disubstituted lower-rim calixarene ligands, including new axially vaulted chiral hemispherical calixarene catalysts based on phosphite substituents, and demonstrate their catalytic utility for MPV reduction.

RESULTS AND DISCUSSION

Our investigation of asymmetric MPV reduction used previously reported enantiopure chiral hemispherical calix[4]arene ligands 1a-1c, shown in Table $1,^9$ in which the asymmetric carbon is directly attached to the calixarene lower rim. We synthesized Al(III) complexes 2a-2c using these ligands (Table 1). This was accomplished by treating 1a-2cwith 1 equivalent (with respect to calix[4]arene diol) of trimethylaluminum in toluene at room temperature for 3 min, followed by the addition of 4 equivalents (with respect to ketone substrate) of secondary alcohol as MPV reductant. Table 1 lists yields and enantioselectivity as measured by chiral gas chromatography for MPV reduction of 2-chloroacetophe-

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Table 1. Asymmetric MPV Reduction with ChiralCalix[4]arene Ligands

| | ЮН | ¶ −0 R | 1. Me₃Al in toluene 2. R₃OH | O-R* | |
|---|----------------------|--------------|--|----------|----------|
| 1a: R*=Ph(| (CH ₃)C* | н | | | R^3 |
| 1b : R*=Nph(CH ₃)C*H | | | | 2a | , 2b, 2c |
| 1c: R*=Ph | (CH ₂ CI) | C*H | | | |
| | Ph | CI | 10 mol% 2 , rt anhy. toluene, 5eq ^{sec} BuOH | OH CI | |
| | Entry | Catalys | t Yield(%) | ee (%) | |
| | 1 | 2a | 100 ^a | <5 | |
| | 2 | 2b | 70 | 20 | |
| | 3 | 2c | 100 ^a | 40 | |
| ^a conversion measured by GC | | | | | |
| ^a Conversion | n meas | ured by | GC | | |

none at room temperature, when using a chiral hydride donor consisting of (S)-2-butanol. Data show that when increasing the steric bulk of the catalyst, lower-rim substituents from α -phenyl methyl in 1a to α -naphthyl methyl in 1b, the enantioselectivity of reduction modestly increased from barely detectable levels up to 20%, as shown by entries 1 and 2, respectively, in Table 1. Such a result is consistent with our previous correlation of greater degree of chirality transfer throughout the calix [4] arene scaffold, as quantified by the geminal coupling constant corresponding to the splitting of calix[4] arene diastereotopic bridging hydrogens,^{14–17} when using more bulky and conformationally rigid lower-rim substituents. On the basis of this correlation, we attempted to increase enantioselectivity further by increasing the rigidity of the calix[4]arene lower-rim substituents. We hypothesized that specific dative interactions between the Al(III) site and lower-rim substituents might be beneficial in this regard and therefore incorporated a Cl substituent in ligand 1c, which was hypothesized to facilitate a noncovalent Cl---Al interaction in complex 2c. This hypothesis was based on a previous demonstration of the catalytic significance of Cl---Al interactions in MPV reduction reactions, which were hypothesized to account for nearly an 8-fold increase in MPV reduction catalytic rate and were supported by single-crystal X-ray diffraction data as well as density-functional theory-based molecular modeling.^{7,8} Entry 3 of Table 1 using catalyst 2c shows an increase in the ee to 40% for the same model reaction. This result in conjunction with entries 1 and 2 in Table 1 clearly demonstrates the catalyst structural features that control enhancement of MPV reduction enantioselectivity and specifically highlights the crucial role of lower-rim calixarene substituent rigidification in this process. No ee was

observed for the reaction and catalysts in Table 1, when using isopropanol as a hydride donor instead of the chiral alcohol.

Guided by the observation above of increasing MPV reduction enantioselectivty upon incorporation of noncovalent contacts when using catalyst 2c, we aimed to further increase MPV reduction enantioselectivity using even more bulky phosphite lower-rim substituents, which are derived from axially chiral diol ligands. Our approach involved the design and synthesis of catalysts 3a-3e in Table 2. The phosphite in these catalysts is directly attached to the calixarene lower rim and provides a Lewis base consisting of the phosphorus lone pair in proximity to the Lewis acid Al(III) center. ³¹P NMR spectroscopy of the ligands before and after complexation with Al does not show evidence of a P…Al interaction (i.e., treatment with Me₃Al in toluene failed to show characteristic shifts in the ³¹P NMR resonance of the phosphite that would be indicative of direct communication of a phosphorus lone pair with aluminum). This may suggest that the phosphorus and Al comprise a frustrated Lewis pair. Similar frustrated Lewis pairs have been previously shown to bind and activate hydrogen as well as transfer hydrogenation catalysts.^{10–13} We hypothesized that the frustrated Lewis pair in our system may also act to facilitate asymmetric hydride transfer in the MPV reduction, when using catalysts 3a-3e. Related benzyl- and fluorenylcapped lower-rim disubstituted calix[4]arene phosphite ligands have been previously reported and have been used as ligands for asymmetric catalysis, in which transition metals have been complexed within a chiral hemispherical cavity on the lower rim of a calix[4] arene macrocycle. $^{t_{4-17}}$ Crucially, in contrast to these previously reported calixarene ligands, those used for synthesis of complexes 3a-3e consist of calix[4]arene lowerrim OH groups, which are available for direct covalent attachment to the Al(III) metal center.

The design and synthesis of 3a-3e is modular insofar as it can be expanded to include a variety of chiral metal complexes, when using other enantiopure phosphites derived from commercially available chiral diols, as well as achiral diols. The synthesis of catalysts 3a-3e is accomplished according to Table 2, by treating unfunctionalized *tert*-butylcalix[4]arene with a toluene solution consisting of two equivalents of enantiopure chlorophosphite. This mixture was stirred overnight at room temperature, in the presence of excess triethylamine, and the reaction was followed using ³¹P NMR spectroscopy. The chlorophosphite was synthesized in a previous step without isolation, according to literature precedent,¹⁸ by treating the corresponding enantiopure BINOL with PCl₃ in the presence of excess triethylamine in toluene (monitored via ³¹P NMR spectroscopy). The synthesis of 3a-3e crucially proceeds with the calix [4] arene adopting a cone conformation according to ¹H and ¹³C NMR spectroscopies. This conformation is preferred because it is the one that leads to a hemispherical cavity on the lower rim, which can serve as a chiral pocket during catalysis.

Table 2 shows the results of the asymmetric MPV reduction when using catalysts 3a-3e, isopropanol as a secondary alcohol hydride donor, and various substituted acetophenones. To the best of our knowledge, the 99% ee achieved with catalyst 3aand *ortho*-fluorobenzophenone as a ketone reactant represents the highest ee reported for Al-catalyzed asymmetric MPV reduction catalysis, when using an achiral alcohol as a hydride donor. At higher fractional conversions approaching 0.8, the ee of this reaction decreases to 80% ee when using 3a as a catalyst. Changing the ketone reactant to *ortho*-chloroacetophenone Table 2. Asymmetric MPV Reduction through Distally Positioned Chiral Substituents in Calix[4]arene Ligands



^{*a*}Reaction conducted at 0 °C.

entry

resulted in a lower ee of 40% under otherwise identical conditions in entry 4 of Table 2. This was increased up to 60% ee by decreasing the temperature from room temperature to 0

 $^{\circ}$ C in entry 3 of Table 2. Catalyst 3a shows poor enantioselectivity for slightly smaller ketones that lack halogen substituents, as shown by acetophenone reduction, which has

% ee

60^a

almost no ee. This result is unlikely to be due to any possible two-point ketone binding to the active site, since we previously demonstrated that such more rigid two-point versus one-point binding is not an attribute that leads to higher enantioselectivity. $5^{-7,19,20}$ It is interesting to note that F ketone entries in Table 2 show high enantioselectivity despite what we previously hypothesized to be much weaker F...Al interactions relative to Cl---Al interactions, and Cl ketones in Table 2 show lower enantioselectivity.⁷ The latter hypothesis was based on a comparative analysis of substituted ketones and their catalytic activity for MPV reduction, which demonstrated enhanced catalytic rates for Cl-substituted versus either F- or Hsubstituted ketones. The latter two types of ketones showed similar MPV reduction activity and were inferred to bind weaker as a result of this.⁷ Here, when using MPV enantioselectivity rather than rate as a probe, it is likely that other factors besides halogen...Al interactions play a role for causing high enantioselectivity. These could include the presence of a chiral pocket that is formed by lower-rim calixarene substituents for catalysts in Table 2. Previously, we demonstrated that the presence of such a pocket acted to decrease the MPV reduction rate for bulkier substrates as well as when using bulky lower-rim substituents.⁷ If cavity effects are important, the data in Table 2 suggest that the right sterically tight fit, which is correlated with lower activity and yield, results in higher enantioselectivity. Such a result is consistent with the relatively poor observed MPV reduction activity when using catalyst 3a and enantioselective recognition in other supramolecular host pockets, in which guests binding more tightly into hosts exhibit a greater degree of stereoselective discrimination.²¹

The degree of π -delocalization of the P lone pair was decreased in DINOL- and TADDOL-derived phosphite catalysts in entries 5 and 6 of Table 2, respectively, which both lack direct aryl oxygen-P connectivity in catalysts **3b** and **3c**, respectively. This delocalization may be important for electronic transmission of chiral information to the metal center. Consistent with this and in contrast, VANOL-derived phosphite catalyst **3d** possesses extended π -delocalization, and this catalyst exhibits both good yield and enantioselectivity in entry 7 of Table 2. Yet if delocalization is too great, as in (*R*)-VAPOL-based catalyst **3e**, this may hamper the electronic communication and results in lower enantioselectivity in entry 8 of Table 2 when using this catalyst relative to **3d**.

In summary, a chiral cavity alone is insufficient for enantioselective hydride delivery in MPV reduction, when using chiral Al(III)-calix[4] arene complexes, since catalysts 2a-2c possessing only a chiral pocket, even a rigidified one as in 2c, are unable to perform asymmetric MPV reduction, when using achiral 2-propanol as a hydride donor. The directed lone pair of the Lewis basic P on the calixarene-phosphite substituent clearly plays a significant role in direct asymmetric hydride delivery to a ketone in the absence of a chiral alcohol hydride donor, when using catalysts 3a-3e. We hypothesize that directed chirality of the phosphite P works synergistically with the presence of a chiral hemispherical pocket, as defined by calix[4] arene lower-rim substituents for directing asymmetric MPV reduction catalysis.

ASSOCIATED CONTENT

S Supporting Information

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Notes

The authors declare no competing financial interest.

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